mantles, and Al-, Ca-, and Si-rich crusts. The first melt that forms when a planetary mantle is sufficiently heated is chemically different from the bulk mantle composition. It is rich in $Al_2O_3$, CaO, $Na_2O$, and $SiO_2$ and poor in MgO, and will rise to the surface of the planet to form the crust. Planets that underwent core formation and partial mantle melting are "differentiated." (Mantle melting is an ongoing process on a large planet such as Earth.)

Most iron meteorites are cores of differentiated planetesimals. Samples from the mantle or crust of these bodies are not known. There is, however, good evidence that we have meteorites representing the crust of the only known large differentiated object in the inner solar system apart from the terrestrial planets and the Moon: the asteroid Vesta (520 km diameter).

The major element composition of basalts from the Moon, Mars, Venus, Vesta, and Earth are quite similar, except for Na, and to a lesser extent Fe (see the figure). The large variations in Na among basalts of the terrestrial planets (see the figure) reflect a correspondingly large range in the initial volatile element endowment of the planets. Variations in FeO resemble different fractions of oxidized (FeO) and reduced (metallic) Fe in the planets. Comparison with NWA011 (*1*) shows that the major element composition of NWA011 resembles that of basaltic meteorites (eucrites) from Vesta (see the figure). On the basis of this evidence alone, one might conclude that NWA011 is a basalt from Vesta, but this conclusion would be premature.

Yamaguchi *et al.* report that the isotopic composition of oxygen in this meteorite is completely different from that of eucrites. Some variation in the oxygen isotopic composition of samples from a single planet is to be expected, but these variations follow certain trends and are predictable. For example, the increase in $^{18}O$ over $^{16}O$ relative to a terrestrial standard should be about twice that of the $^{17}O/^{16}O$ increase. The oxygen isotopic composition of NWA011 does not follow the trends expected for eucrites. The planet or planetesimal from which NWA011 originated has substantially more $^{16}O$ than does Vesta. Yamaguchi *et al.* conclude that the meteorite comes from an unknown, differentiated planetary object.

A closer look at the major and trace element composition of NWA011 and eucrites shows that despite the similarities, including relatively high Mn contents (see the figure), there are also important differences. NWA011 has a very different rare-earth element pattern, with low rare-earth element content but a pronounced positive Eu-anomaly. Furthermore, the NWA011 meteorite has the highest FeO content of all basalts shown in the figure, and its Ni and Co contents are higher than those of eucrites, while Cr is lower. The high Ir content of NWA011 is unique for a basalt and requires explanation.

These chemical characteristics are inconsistent with NWA011 being a simple partial melt from any planetary mantle. It must have had a more complicated origin involving extensive melting, crystallization, and mixing, but without losing the basaltic major element composition. The high FeO content of NWA011 (see the figure) indicates that its parent planet can only have a small core. A large fraction of the bulk Fe content of the planet is oxidized, contrary to Earth with its large Fe core and its low FeO content in the mantle.

The NWA011 meteorite has basaltic major element composition, mineralogy, and texture, but oxygen isotopic compositions and trace element concentrations rule out a relationship to known basalts of the inner solar system. Perhaps NWA011 is a basalt from Mercury. This is dynamically possible, although the yield is less than 1% of that of martian meteorites (*3*). A better knowledge of the chemical composition of the surface of Mercury is a prerequisite to identifying mercurian meteorites. Alternatively, a much smaller asteroid may have produced basalts of compositions that are so far only known from the larger bodies of the solar system.

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PERSPECTIVES: IMMUNOLOGY

# Pathogen Surveillance—the Flies Have It

**Ranjiv S. Khush, François Leulier, Bruno Lemaitre**

The ancient origins of the battles between infectious microbes and their hosts are illustrated by the similarities in frontline defense adopted by insects and mammals. In mammals, the innate immune system defines a rapidly induced first response to infection that directly activates host defenses and also stimulates the adaptive immune system. Insects share features of the mammalian innate immune response. In both groups, pathogens are recognized through interactions of stereotypical microbial structures with host proteins called pattern recognition receptors (*1*). Mammalian pattern recognition receptors include the Toll-like receptors (TLRs), so-called because they resemble the Toll receptor of *Drosophila*. The Toll receptor and the TLRs activate immune responses to infection that are regulated by the transcription factor NF-κB. However, unlike the TLRs, Toll does not interact directly with microbial compounds such as lipoproteins or peptidoglycans. Consequently, the identity of pattern recognition receptors in *Drosophila* has posed a compelling puzzle. This puzzle has been partly resolved with the reports by Choe and colleagues on page 359 of this issue (*2*) and Michel *et al.* in *Nature* (*3*). These investigators identify two peptidoglycan recognition proteins (PGRPs) in the fruit fly that are probable pattern recognition receptors for the insect innate immune response.

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R. S. Khush is in the Department of Microbiology and Immunology, Stanford University School of Medicine, Stanford, CA 94305, USA. F. Leulier and B. Lemaitre are at the Centre de Génétique Moléculaire, CNRS, 91198 Gif-sur-Yvette, France. E-mail: lemaitre@cgm.cnrs-gif.fr

The *Drosophila* Toll receptor signaling pathway was initially implicated in the specification of dorsoventral polarity during embryonic development. Subsequently, several components of this pathway were found to be necessary for resistance to fungal infection. Upon fungal infection, Toll proteins on the surface of fat-body cells (the insect equivalent of the liver) are activated by a proteolytically cleaved form of an extracellular cytokine-like protein, Spaetzle, which is present in insect hemolymph (blood). Interactions between Spaetzle and Toll trigger an intracellular signaling cascade that culminates in the nuclear translocation of two NF-κB–like transactivators, Dorsal and Dif, which induce expression of genes encoding antimicrobial peptides (*4, 5*) (see the figure). Similarities between the Toll receptor pathway and the interleukin-1 receptor pathway, which regulates

mammalian immune responses, revealed evolutionary links between *Drosophila* and mammalian innate immunity, facilitating the identification of TLRs in mammals.

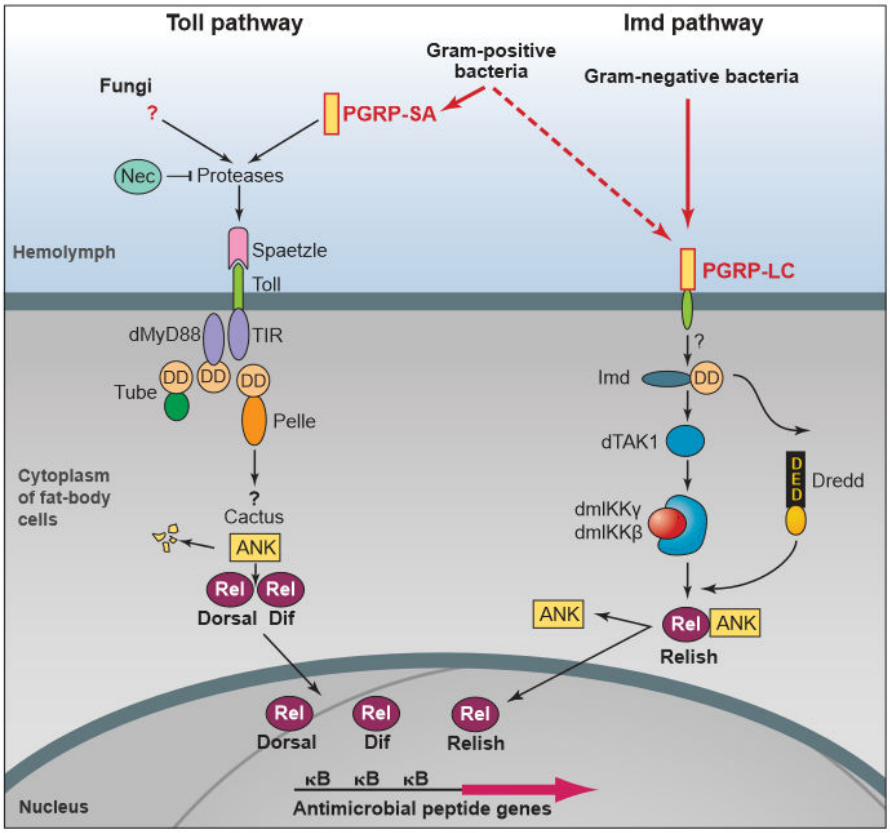
The *Drosophila* immune deficiency (Imd) pathway is a second independent signaling cascade in fat-body cells that fights Gram-negative bacteria (see the figure) (*4, 5*). In contrast to the Toll pathway, the Imd pathway is not involved in development. This finding has facilitated the identification of additional components of this pathway through genetic screens. The Imd pathway induces antimicrobial gene expression via a third *Drosophila* NF-κB–like factor, Relish. It shares some similarities with the mammalian tumor necrosis factor receptor pathway, pointing to evolutionary conservation between these two signaling cascades.

In vertebrates, multiple TLRs enable detection of different microbial compounds. TLR4, for example, activates immune responses to the lipopolysaccharides (LPS) that are found in Gram-negative bacterial cell walls. In contrast, TLR2 mediates responses to peptidoglycan, a major component of the cell walls of Gram-positive bacteria (*6*). The presence of pathogen-specific pattern recognition receptors in *Drosophila* is clearly indicated by the preferential activation of the Toll pathway by fungal and Gram-positive bacterial infections and the activation of the Imd pathway by Gram-negative bacteria. In addition, the *Drosophila* genome encodes eight Toll homologs, suggesting that fruit flies may use different Toll receptors to differentiate among pathogens. Nevertheless, studies of these proteins in cultured cells have not demonstrated their involvement in microbial recognition. Thus, our understanding of pathogen detection in insects has lagged behind that in mammals.

The facility of genetic screens for isolating immunocompromised *Drosophila* mutants is closing this gap. Michel *et al.* (*3*) started to search for fly mutations that block antimicrobial gene expression induced by Gram-positive bacteria. They found that Gram-positive bacterial infections activate PGRP-SA, a protein circulating in the fly hemolymph that then activates the Toll pathway. PGRPs were initially isolated from the moths *Bombyx mori* and *Trichoplusia ni* because of their high affinity for bacterial peptidoglycan (*7, 8*). Mutations in PGRP-SA block the activation of the Toll pathway in response to Gram-positive bacteria and significantly decrease resistance to this type of infection, in perfect agreement with the prediction that this protein detects the peptidoglycan in Gram-positive bacterial cell walls. The steps that link PGRP-SA and the Toll ligand Spaetzle are not known, but they probably involve serine proteases because a serine protease inhibitor, Necrotic, represses Toll activation. Mutations in PGRP-SA do not affect Toll activation induced by fungal infection, indicating that additional fungal-specific pattern recognition receptors may act upstream of Toll. Interestingly, the *Drosophila* genome contains 12 additional *PGRP* genes that are predicted to encode either short extracellular proteins (like PGRP-SA) or longer intracellular and membrane-spanning proteins (*9*). PGRP-SA's involvement in Gram-positive bacterial recognition, together with the large number of PGRP proteins in flies, suggests that this family mediates the recognition of multiple microbial species.

Results from a second genetic screen provide support for this hypothesis. Choe *et al.* (*2*) demonstrate that fly mutations—originally isolated in a search for genes that induce antimicrobial gene expression after Gram-negative bacterial infection—affect the *PGRP-LC* gene. These results have been confirmed by two other groups using different approaches (*10*, *11*). *PGRP-LC* is predicted to encode a transmembrane protein with an extracellular PGRP domain. This protein activates the nuclear translocation of Relish and antimicrobial gene expression via the Imd pathway after both Gram-negative and Gram-positive bacterial infection. Although the localization of PGRP-LC in fat-body cell membranes and its direct interaction with microbial compounds has yet to be demonstrated, these genetic results suggest that PGRP-LC is a pattern recognition receptor for the Imd pathway in flies.

The demonstration that PGRPs operate in both the Toll and Imd pathways clarifies several aspects of insect immunity. First, it is now clear that *Drosophila* has two different systems for sensing microbes: (i) circulating pattern recognition receptors such as PGRP-SA that are present in the hemolymph (the Toll pathway), and (ii) transmembrane recognition receptors such as PGRP-LC (the Imd pathway) (see the figure). One obvious advantage of circulating recognition molecules is that they are able to sense microbes throughout the body cavity and to amplify signals via proteolytic signaling cascades. Extracellular signaling proteins, however, require enclosed compartments and cannot work in tissues exposed to the external environment. This may explain why the Imd pathway is the predominant cas-




**Invaders pay the Toll.** The Toll and Imd pathways regulate the *Drosophila* antimicrobial innate immune response. Antimicrobial peptide genes are regulated by the NF-κB–like proteins Dif, Dorsal, and Relish, which are the end targets of two distinct signaling cascades: The Toll pathway, which is principally activated by fungi and Gram-positive bacteria, and the Imd pathway, which is largely activated by Gram-negative bacteria. PGRP-SA is a circulating protein required for Toll activation in response to Gram-positive bacteria (*3*). PGRP-LC is a putative pattern recognition receptor required for the activation of the Imd pathway (*2*).

cade regulating the expression of antimicrobial peptide genes in exposed tissues such as the trachea and the gut (*4, 5*). Second, it has been established that the Toll and Imd pathways are differentially activated by different microbes. Therefore, the presence of recognition proteins with PGRP domains in both pathways suggests that the PGRP domain may exhibit multiple binding specificities (like the extracellular leucine-rich repeat domain found in all TLRs). The existence of distinct recognition properties could explain the large number of *PGRP* genes in the fly genome, although it is probable that some of them control other immune reactions like the prophenoloxidase cascade, which has been described in *Bombyx* (*7*).

That PGRPs work in both the Toll and Imd pathways also highlights several aspects of insect immunity that are not understood. Foremost is the nature of the microbial compounds that are recognized by the insect immune system. Direct injection of LPS into flies does not induce a strong immune response or any toxic shock–like reaction, which suggests that the fly immune system is less sensitive to LPS than is the mammalian innate immune system. The ability of PGRP-LC to recognize Gram-negative bacteria also suggests that Gram-negative bacteria are not recognized because of their LPS but perhaps through another molecular pattern such as a specific form of peptidoglycan. Alternatively, as suggested by Choe *et al.*, PGRP-LC might bind to both peptidoglycan and LPS, or cooperate with other proteins as part of a recognition complex. Further studies will have to reconcile these apparent contradictions and identify the precise microbial compounds recognized by these pattern recognition receptors.

The growing appreciation of the conservation of some immune responses in insects and mammals has produced an exchange of ideas and results that has invigorated the field of innate immunity. The discovery of the involvement of NF-κB in *Drosophila* antimicrobial gene expression was stimulated by the recognized importance of NF-κB in mammalian immunity. The identification of the Toll receptor as a mediator of insect immunity directed attention to the mammalian TLR proteins. Now, the identification of PGRPs as pattern recognition receptors in insects points to the importance of these proteins in mammalian immunity (*12*). Mechanisms of host defense shared by insects and mammals highlight the value of genetics to the study of immunity. Several years ago, it was generally felt that, in contrast to developmental processes that are tightly regulated, genetic analyses of immune systems would be hampered by functional redundancies among protein components of immune pathways. Mutations in *Drosophila* and mouse proteins, however, reveal that disrupting genes that belong to large families, such as those encoding TLRs and PGRPs, can generate specific immune defects. Such results validate this approach in the ongoing dissection of the battle between pathogens and their hosts.

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PERSPECTIVES: PLANT BIOLOGY

# MADS-Box Genes Reach Maturity

**Barry Causier, Martin Kieffer, Brendan Davies**

Since Adam's first visit to the fruiteress in the Garden of Eden, humankind has been totally dependent upon the angiosperm flower and the fruit it bears. Much of our food and clothing is derived from flowers and their fruits. Unraveling the pathways that regulate how flowers, fruits, and seeds develop has significant implications for agriculture. Ripening is a vital aspect of fruit production. For many fruits to be palatable they must be fully ripe, and ripening is essential for propagation of the species. In terms of shipping, storage, and shelf life, we need to know how to control the ripening of edible fruits. On page 343 of this issue, Vrebalov *et al.* (*1*) reveal that a tomato plant whose fruit cannot ripen, called *ripening-inhibitor* (*rin*), carries a mutation in a gene encoding a MADS-box transcription factor. This work not only establishes the involvement of MADS-box factors in fruit ripening, but also has important agricultural implications.

In today's world of global distribution, the control of fruit ripening is of strategic importance. Unfortunately, our understanding of the genetic regulation of ripening is limited, reducing our ability to manipulate this process. In the tomato and many other fruits, early ripening events involve an increase in biosynthesis of the plant hormone ethylene accompanied by a burst of respiration. The fruit then undergoes a complex and coordinated transformation (*2*). Cell wall structure is modified, improving texture and inducing softening (see the figure). The production of compounds conferring flavor and aroma increases. Starch is converted into sugars, adding sweetness, and red pigments (such as carotene and lycopene) begin to replace the green chlorophyll. Ethylene signaling is one of the best known plant hormone regulatory pathways (*3*) and is a key factor in the control of ripening. However, developmental pathways also influence ripening, and many types of fruit do not require increased ethylene biosynthesis to ripen. So far, an overall developmental regulatory pathway, common to all fruit, has remained elusive.

Successful attempts to manipulate ripening have centered on either reducing ethylene production to slow down the process, or decreasing the rate of fruit softening (*4*). Fruit with reduced ethylene production can be ripened by artificial exposure to ethylene. Unfortunately, fruits that do not depend on increased ethylene production for ripening are not amenable to this approach. Reduced softening has been achieved by altering the expression of genes involved in cell wall modification. The best known example is the "Flavr Savr" tomato, in which shelf life was increased by reducing the level of the enzyme polygalacturonase. One limitation of this approach is that different genes will need to be altered to reduce softening in different fruits (*5*). Discovering a presumptive developmental pathway that is conserved between all types of fruits would create new opportunities for controlling fruit ripening.

Characterization of the *rin* mutation by Vrebalov and colleagues (*1*) could mark a turning point. Tomato plants carrying the *rin* mutation are blocked at an early stage in the ripening process, before the respiratory burst, and do not ripen in response to ethylene. The *rin* tomato plant also has enlarged sepals and an altered inflorescence architecture. Vrebalov *et al.* show that the *rin* mutation is caused by a deletion of approximately 3 kilobases of DNA from the

The authors are at the Centre for Plant Sciences, University of Leeds, Leeds LS2 9JT, UK. E-mail: b.h.davies@leeds.ac.uk